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ARTERIAL BLOOD GASES, PULMONARY FUNCTION AND PATHOLOGY IN RATS EXPOSED TO 0.75 OR 1.0 ppm OZONE

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Arterial blood gases, residual lung volume (RV), deflation pressure volume (PV) curves, pulmonary pathology and body weight changes were studied in rats exposed up to 14 days to either 0.75 or 1.0 ppm ozone. Arterial PO_2 and body weights decreased progressively with length of exposure while $PaCO_2$ and RV increased. The slope of the PV curve decreased in all groups exposed to ozone. Pathological changes in the lung increased in severity with concentration and length of exposure. The present findings have shown that arterial blood gas measurements represent a sensitive index of altered lung function in rats, a species very sensitive to ozone exposure.

INTRODUCTION

Numerous experiments have been conducted in order to evaluate the toxicological effects of ozone in experimental animals. Examples of such studies have included voluntary running activity (Fletcher and Tappel, 1973), neurophysiological responses (Eglite, 1968; Xintaras *et al.*, 1966), morphological changes in the lungs (Freeman *et al.*, 1974; Stephens *et al.*, 1974), pulmonary edema (Alpert *et al.*, 1971) and enzyme concentrations (Castleman *et al.*, 1973; Chow *et al.*, 1974). There is no information available, however, relating the effects of ozone exposure upon arterial blood gases. Since the primary function of the lungs is to provide for gas exchange, such measurements would be extremely useful in assessing the toxic effects of ozone as well as other gaseous pollutants.

Blood gas measurements have not been conducted to any appreciable degree in the past because of the difficulty in sample collection from conscious, relatively undisturbed, small laboratory animals. This limitation has largely been overcome with the development of a technique for collecting arterial blood from the Caudal artery in rats (Pepelko and Dixon, 1975). The objective of the present study was to measure arterial blood PO_2, PCO_2 and pH in fully conscious rats following exposure to ozone for up to 14 days and to compare

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the results with changes in lung volume, static compliance and pulmonary pathology.

MATERIALS AND METHODS

Young adult male Sprague-Dawley rats averaging 335 grams at the start of the experiment were housed in wire cages, 2 animals per cage. Feed and water were provided *ad libitum*. The animals were exposed in stainless steel chambers 1 meter square with an interior volume of 1.27 m^3. Airflow through the chamber was regulated at a rate equivalent to 4 changes per hour. Ozone was produced with a generator designed and constructed in-house. High voltage neon tubes were connected in opposing pairs discharging a silent arc across a transformer. The transformer output was controlled by a rheostat allowing up to 15,000 volts for the silent discharge. Oxygen was passed over the field at 2 liters/minute. Ozone concentration in the chamber was monitored continuously with a Meloy model OA 350 Ozone Analyzer.

Twelve rats each were exposed to either clean filtered air, 0.75 ppm ozone or 1.0 ppm ozone for 1, 3, 7 or 14 days. The exposures were continuous except for short periods when the chamber was opened for cleaning cages, removal of animals, etc. Due to a high mortality rate among rats exposed for 14 days to 1.0 ppm ozone, additional rats were added to this group until 10 survivors were obtained.

After exposure the rats were removed individually from the chamber, weighed, briefly anesthetized with sodium thiamyl (40 mg/kg intravenously) and a polyethylene catheter implanted into the caudal artery. Upon recovering consciousness an arterial blood sample was collected. The rat was then placed in a small translucent chamber with the arterial catheter and a rectal temperature probe ducted to the exterior. The chamber was flushed with 100% 0_2 and a second arterial blood sample collected after 10 minutes. The chamber was then flushed with gas containing 9% 0_2, and 91% N_2 for an additional 10 minutes. A final blood sample was collected near the end of this exposure. Arterial blood pH, PCO_2 and PO_2 were measured immediately after blood collection using an Instrumentation Laboratories model IL213 blood gas analyzer. Additional details of the procedure have been published previously (Pepelko and Dixon, 1975).

Following completion of blood collection the rats were again anesthetized using sodium pentobarbital (45 mg/kg). A cannula was then ligated into the trachea. The rat was placed in a sealed plethysmograph with the cannula ducted to the exterior. The animal was forced to expire maximally by suddenly increasing the plethysmograph pressure to 60 cm H_2O. The volume of air remaining in the lungs was considered to be equal to residual volume (RV). Following maximal expiration ten cc of a gas mixture containing 10% He in air was injected into the lungs. After 10 seconds an identical volume was withdrawn and the helium content analyzed using a Perkin Elmer model MGA 1100 medical gas mass spectrometer. Residual volume was calculated by dilution of helium. A mean of 3 measurements was calculated for each rat. No correction was made for dead space.

After measurement of RV, pure oxygen was administered for 3 minutes. The animal was then asphyxiated by occluding the tracheal cannula, allowing total collapse of the lungs. A ventral incision was made through the sternum and the chest wall retracted with hemostats. The aorta and vena cava were cut in order to drain as much blood from the lungs as possible. The lungs were filled with air to a pressure of 30 cm H_2O, allowing 2 minutes for pressure to stabilize. Following inflation the lungs were deflated stepwise in pressure increments of 3 cm H_2O and volume was recorded. The final recording was at ambient pressure. Deflation curves of transpulmonary pressure versus percent of total lung volume were plotted for each exposure group.

After completion of the pressure volume maneuver, the lungs were removed, weighed and filled with a 10% solution of buffered formalin to a pressure of 30 cm H_2O. The trachea was ligated after a minimum of 15 minutes and the lungs stored in buffered formalin until sectioned. Slides were prepared and the lungs examined for evidence of pathology.

RESULTS

Body weight changes during ozone exposure are shown in Fig. 1. Each data point represents a comparison of pre and post exposure weights for individual groups of animals. The data were analyzed by analysis of variance. Duncan's multiple range test was used to detect mean differences among groups at each time of exposure. Differences were considered significant if a p value of .05 or less was obtained. After one day the control group lost an average of 10 grams followed by gains of 11, 19 and 51 gms after 3, 7 and 14 days respectively. Exposure to 0.75 ppm ozone resulted in losses of 33, 23, 19 and 41 gms after 1, 3, 7 and 14 days respectively. Exposure to 1.0 ppm ozone resulted in losses of 24, 21, 25 and 72 gms after 1, 3, 7 and 14 days respectively. Both concentrations of ozone resulted in significant decreases in body weight compared with controls at all exposure durations. In addition, a larger decrease in body weight occurred in rats exposed for 14 days to 1.0 ppm ozone compared with 0.75 ppm ozone.

Arterial blood gas and pH measurements are listed in Tables 1, 2 and 3. The changes in PaO_2 and $PaCO_2$ due to breathing ozone are shown in Fig. 2. Means for each parameter collected from animals exposed to 0.75 or 1.0 ppm ozone were compared statistically with those from animals exposed to clean air at the indicated length of exposure. Differences were considered significant if a p value of .05 or less was obtained.

Arterial blood PO_2 of the control animals averaged near 90 torr at all 4 exposure times. Exposure to either 0.75 or 1.0 ppm ozone resulted in progressive decreases in PaO_2 with length of exposure. The means differed significantly from controls after 7 and 14 days exposure to 0.75 ppm ozone. Differences approached significance after one day and attained significance after 3, 7 and 14 days exposure to 1.0 ppm ozone. Differences among groups could no longer be detected during 10 minutes inspiration of 100% O_2. During inhalation of 9% O_2, PaO_2 values significantly lower than controls were detected for

rats previously exposed to 1.0 ppm ozone for 3, 7 and 14 days and 0.75 ppm ozone for 14 days.

TABLE 1. Arterial blood PO_2 in rats previously exposed up to 14 days to either clean air, 0.75 ppm ozone or 1.0 ppm ozone.

	AIR[4]		
Days Exposure	Control[3] (torr)	0.75 ppm[3] (torr)	1.0 ppm[3] (torr)
1	89.3 ± 4.9[1]	88.3 ± 4.7	81.5 ± 5.6
3	90.5 ± 5.9	86.4 ± 5.8	73.8[2] ± 13.3
7	90.2 ± 5.9	74.5[2] ± 10.1	63.9[2] ± 15.2
14	91.1 ± 5.5	66.7[2] ± 4.5	50.9[2] ± 12.0
	100% O_2		
Days Exposure	Control (torr)	0.75 ppm (torr)	1.0 ppm (torr)
1	411 ± 63	441 ± 34	441 ± 55
3	460 ± 60	486 ± 30	427 ± 65
7	410 ± 55	417 ± 60	381 ± 104
14	419 ± 85	437 ± 75	408 ± 94
	9% O_2		
Days Exposure	Control (torr)	0.75 ppm (torr)	1.0 ppm (torr)
1	30.1 ± 4.8	29.5 ± 2.6	25.7 ± 3.5
3	31.0 ± 4.7	29.3 ± 3.1	25.2[2] ± 3.5
7	30.7 ± 4.5	29.3 ± 3.2	24.0[2] ± 2.2
14	30.7 ± 2.7	25.3[2] ± 2.7	24.5[2] ± 4.6

[1] ± one standard deviation
[2] Significantly different from control $P<.05$
[3] N = 10 for all groups
[4] Each animal in every group was exposed to room air, 100% O_2 and 9% O_2 for successive 10 minute periods. Blood samples were collected near the end of each period.

Increases in $PaCO_2$ while breathing air were detected in rats previously exposed to either 0.75 or 1.0 ppm ozone for 7 or 14 days. Significant increases compared with controls were also noted in groups previously exposed to 0.75 ppm for 14 days and 1.0 ppm ozone for 7 or 14 days while breathing 100% O_2. During inhalation of 9% O_2 $PaCO_2$ values greater than controls were detected in groups exposed 7 and 14 days to 0.75 ppm ozone and 14 days to 0.75 ppm ozone.

Arterial blood pH levels, in general, showed smaller changes than PaO_2 or $PaCO_2$. A significant arterial blood pH increase was detected in animals

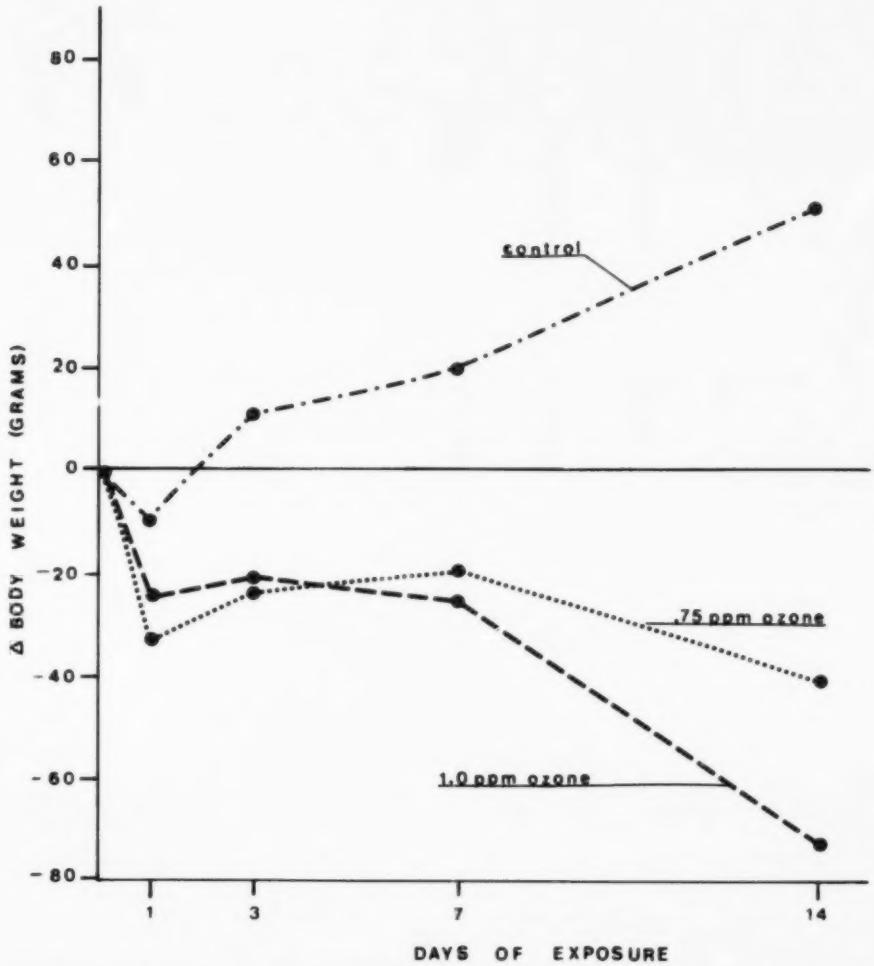

FIGURE 1. Body weight changes during exposure to either 0.75 or 1.0 ppm ozone. Each data point represents the difference between initial and final weights for individual groups of animals.

exposed to 0.75 ppm ozone for one day. Following 14 days exposure to 1.0 ppm ozone significant decreases in arterial blood pH compared with controls were detected while breathing air, 100% O_2 or 9% O_2. A significant decrease in pH was also noted in groups previously exposed to 0.75 ppm ozone for 7 or 14 days while breathing 9% O_2.

RV, total lung capacity (TLC) and lung weights are shown in Table 4. The means for TLC, RV, and lung weight following exposure of the animals to 0.75 or 1.0 ppm ozone were compared statistically with those from animals exposed to clean air at the indicated length of exposure. Differences were

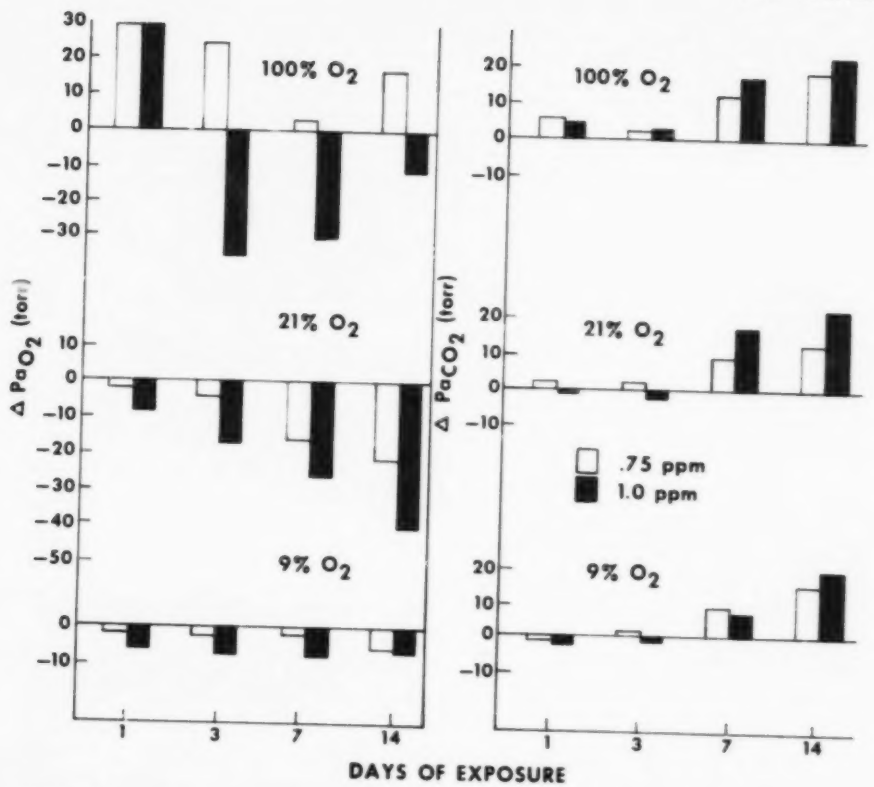

FIGURE 2. Changes in arterial blood PO_2 and PCO_2 during exposure to either 0.75 or 1.0 ppm ozone. Each data point represents the difference between ozone exposed rats and clean air rats at the indicated length of exposure.

considered significant if a p value of .05 or less was obtained. RV increased progressively with length of exposure at either concentration of ozone. Significant increases ($P<.05$) were detected after 7 days or 14 days exposure to both 0.75 and 1.0 ppm ozone. TLC and deflation PV curves were not measured on rats exposed to 1.0 ppm ozone due to fragility of the lungs causing frequent ruptures. The only difference detected in TLC was an increase after 14 days exposure ($P<.05$). Lung weights of rats exposed to 0.75 ppm ozone did not differ significantly from controls, while those exposed for 1, 3 and 7 days to 1.0 ppm ozone showed a significant increase ($P<.05$).

Deflation PV curves for rats exposed to 0.75 ppm ozone are shown in Fig. 3. Since the curves for the 4 control groups were nearly identical they were averaged to simplify the graph. In order to test for differences among the curves, the data was fitted to the equation $\ln Y = a + bx$ where Y = percent of TLC and x = pressure in cm H_2O. The calculated slope for all control groups averaged 0.058 compared with 0.032, 0.032, 0.035 and 0.040 for groups exposed for 1,

3, 7 and 14 days respectively. The slopes at all 4 exposure times differed significantly from that of controls ($P<.001$). The calculated intercept for all control groups averaged 3.37 compared with 3.94, 3.93, 3.87 and 3.78 for groups exposed for 1, 3, 7 and 14 days respectively. Again, the differences between controls and all 4 experimental groups were highly significant ($P<.001$). The actual measured lung volume at ambient pressure as a percent of TLC averaged 13.3 for all controls compared with 34.3, 32.8, 31.9 and 29.6 for the groups exposed 1, 3, 7 and 14 days to 0.75 ppm ozone. The means at each exposure time differed significantly from that of controls ($P<.001$).

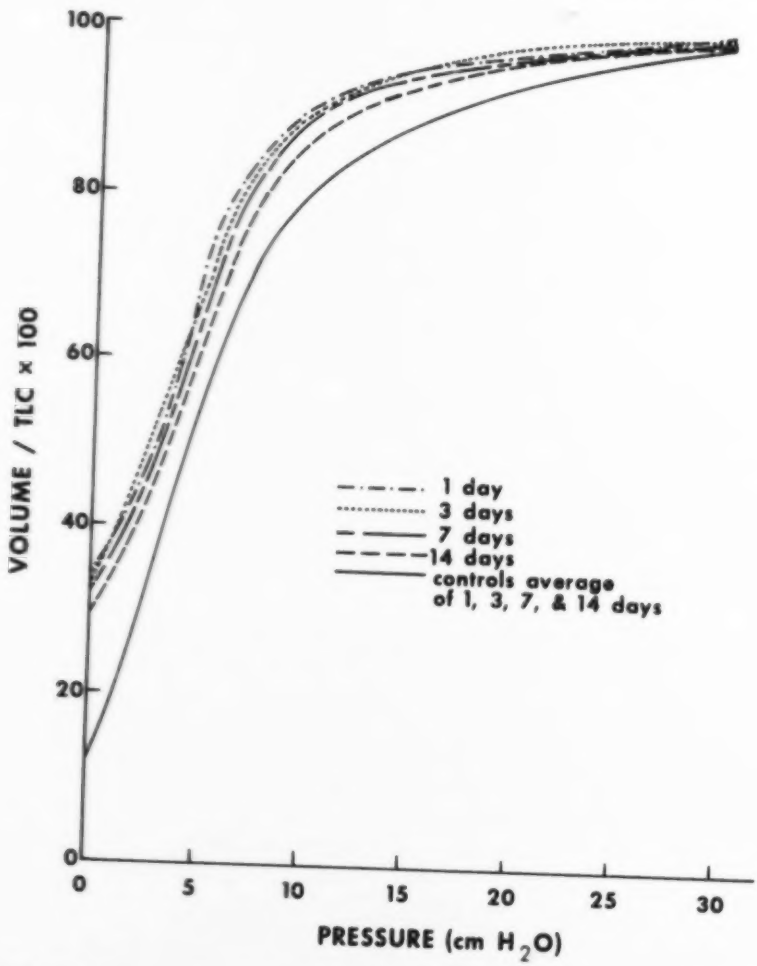

FIGURE 3. Deflation PV curves for rats exposed to 0.75 ppm ozone. Data from each group was fitted to the equation $\text{Ln } Y = a + bx$ where Y = percent of TLC and x = pressure in cm H_2O. The curves from all 4 control groups were averaged to simplify the figures.

TABLE 2. Arterial blood PCO_2 in rats previously exposed up to 14 days to either clean air, 0.75 ppm ozone or 1.0 ppm ozone.

Days Exposure	Control[3] (torr)	AIR[4] 0.75 ppm[3] (torr)	1.0 ppm[3] (torr)
1	34.8 ± 3.1[1]	36.5 ± 3.7	33.2 ± 5.8
3	35.9 ± 3.8	37.3 ± 2.8	33.1 ± 7.5
7	33.3 ± 4.0	41.6[2] ± 3.2	50.3[2] ± 10.6
14	36.7 ± 3.3	48.6[2] ± 4.0	58.3[2] ± 10.5
Days Exposure	Control (torr)	100% O_2 0.75 ppm (torr)	1.0 ppm (torr)
1	32.9 ± 6.7	37.3 ± 2.6	36.6 ± 6.4
3	35.4 ± 5.3	36.5 ± 3.0	36.6 ± 5.1
7	30.8 ± 5.2	41.7 ± 6.2	46.1[2] ± 7.0
14	34.7 ± 3.7	46.8[2] ± 4.8	56.6[2] ± 21.6
Days Exposure	Control (torr)	9% O_2 0.75 ppm (torr)	1.0 ppm (torr)
1	23.2 ± 4.4	22.6 ± 2.6	21.0 ± 2.8
3	23.0 ± 2.9	24.0 ± 1.6	21.4 ± 4.4
7	22.1 ± 2.7	30.3[2] ± 5.7	28.8 ± 7.5
14	23.1 ± 5.2	37.0[2] ± 6.2	42.6[2] ± 10.9

[1]± one standard deviation
[2]Significantly different from control $P<.05$
[3]N = 10 for all groups
[4]Each animal in every group was exposed to room air, 100% O_2 and 9% O_2 for successive 10 minute periods. Blood samples were collected near the end of each period.

Large differences in lung pathology could not be detected between groups exposed to 0.75 ppm or 1.0 ppm ozone. The severity of effects, however, increased with length of exposure. After one day of exposure focal alveolitis, focal, interstitial thickening and hypertrophy of the alveolar lining cells, subchronic perivasculitis and peribronchiolitis were noted. After three days exposure additional changes included interstitial pneumonitis, proliferative bronchiolitis, metaplastic changes in the trachea and hemorrhage in the bronchial lymph nodes. After 7 or 14 days of exposure proliferative bronchiolitis with focal squamous metaplasia of the terminal respiratory bronchioles occurred.

DISCUSSION

The rat is very susceptible to the toxic effects of ozone, with 0.75 ppm being near the maximum level tolerated for intermediate term survival. Only ten of 29 rats exposed to 1.0 ppm ozone survived for 14 days. The weight loss of

the survivors indicated that even greater mortality rates would be expected with continued exposure. All of the rats exposed for 14 days to 0.75 ppm ozone survived until sacrifice. The decrease in PaO_2 and weight loss, however, indicated that these animals were also under considerable stress and that some mortality would be likely with continued exposure. The present findings are in agreement with those reported in a previous study in which 50% mortality occurred during 3 weeks exposure of 0.9 ppm (Freeman *et al.*, 1974). By contrast, mice survived 18 months of continuous exposure to 1 ppm ozone (Stokinger, 1962).

The decline on PaO_2 following exposure to ozone was shown to be a sensitive indicator of pulmonary dysfunction. Arterial PO_2 decreased steadily with increased length of exposure at either ozone concentration with differences approaching the 5% level of significance as early as one day of exposure. The changes in PaO_2 with concentration and length of exposure to ozone indicated that this parameter was capable of indicating the relative degree of lung damage.

Collection of blood samples during inspiration of altered oxygen concentrations was designed to increase the sensitivity of blood gas measurement. With a decrease in inspired oxygen an increase in ventilation is necessary to maintain a normal PaO_2. If lung damage is such that increased ventilation is required to maintain a normal PaO_2 while breathing room air, or if airflow increases are limited by airway obstruction, then the respiratory response to hypoxia may be less than in normal animals. Significant differences in PaO_2 between control and ozone exposed rats breathing 9% O_2 were detected within 3 days of exposure to 1.0 ppm ozone, and approached significance after 1 day. Progressive decreases in PaO_2 with increasing length of exposure, however, were not seen. Evidently a very strong respiratory response prevented PaO_2 from decreasing below 24 torr even in rats with severe lung damage.

Measurement of PaO_2 during inspiration of 100% O_2 was conducted in order to gain some insight into the nature of the lung dysfunction. One of the primary effects of acute exposure to ozone is pulmonary edema (Scheel *et al.*, 1959). This commonly results in a small decrease in diffusing capacity that can usually be treated effectively with 100% O_2 (Guyton, 1976). If a large number of alveoli or respiratory units are blocked on the other hand due to total filling with fluid, an inequality of ventilation and perfusion of sufficient degree may exist such that PaO_2 remains low even during exposure to pure oxygen. This did not appear to be the case except for a few of the rats exposed to 1.0 ppm ozone. The presence of these animals resulted in slightly lower mean PaO_2 values, but due to the concomitant increase in variability, differences from that of controls were not significant. It was concluded, at least in the present study, that the use of PaO_2 while breathing ambient air was a more useful indicator of pulmonary dysfunction than either increased or decreased oxygen percentages.

Longer exposure times were necessary before differences in $PaCO_2$ could be detected. CO_2 is more diffusible than O_2 and is controlled more closely by the respiratory center. Nevertheless, increases were evident by 7 days exposure to either ozone concentration with even larger increases after 14 days. Arterial

TABLE 3. Arterial blood pH in rats previously exposed up to 14 days to either clean air, 0.75 ppm ozone or 1.0 ppm ozone.

		AIR[4]		
Days Exposure	Control[3] (torr)		0.75 ppm[3] (torr)	1.0 ppm[3] (torr)
1	7.46 ± 0.02[1]		7.51[2] ± 0.04	7.48 ± 0.03
3	7.46 ± 0.02		7.46 ± 0.02	7.46 ± 0.03
7	7.46 ± 0.02		7.45 ± 0.02	7.43 ± 0.05
14	7.45 ± 0.02		7.44 ± 0.02	7.38[2] ± 0.07
		100% O_2		
Days Exposure	Control (torr)		0.75 ppm (torr)	1.0 ppm (torr)
1	7.45 ± 0.04		7.48 ± 0.02	7.48 ± 0.02
3	7.45 ± 0.02		7.45 ± 0.03	7.43 ± 0.03
7	7.46 ± 0.03		7.43 ± 0.03	7.42 ± 0.05
14	7.45 ± 0.02		7.42 ± 0.03	7.36[2] ± 0.06
		9% O_2		
Days Exposure	Control (torr)		0.75 ppm (torr)	1.0 ppm (torr)
1	7.58 ± 0.04		7.61 ± 0.03	7.62 ± 0.03
3	7.57 ± 0.04		7.58 ± 0.05	7.58 ± 0.06
7	7.55 ± 0.10		7.41[2] ± 0.12	7.52 ± 0.08
14	7.59 ± 0.04		7.40[2] ± 0.13	7.38[2] ± 0.10

[1]± one standard deviation
[2]Significantly different from conrol $P<.05$
[3]N = 10 for all groups
[4]Each animal in every group was exposed to room air, 100% O_2 and 9% O_2 for successive 10 minute periods. Blood samples were collected near the end of each period.

PCO_2 remained above that of air breathing controls after 14 days exposure to 1 ppm ozone, even with the additional respiratory stimulus of a hypoxic gas mixture. Arterial pH, in general, reflected changes in $PaCO_2$ with rats becoming acidic as $PaCO_2$ increased.

Among the functional measurements, RV changes correlated most closely with PaO_2. RV was defined as the volume of air in the lungs at a positive plethysmograph pressure of 60 torr. Preliminary testing has shown that greater increases in positive pressure did not result in further decreases in lung volume. Thus it was felt that the volume measured represented a reasonable estimate of lung volume at airway closure. Significant increases in RV were found after 3 days exposure and became progressively larger with length of exposure. After 14 days exposure the group exposed to 0.75 ppm ozone had attained a larger RV than those exposed to 1.0 ppm. The mean of the 1.0 ppm group, however, was undoubtedly distorted by the fact that many of the rats exposed to 1.0 ppm

TABLE 4. The effects of ozone exposure upon residual volume, lung weight and total lung capacity.

Days Exposure	Residual volume (CC)			Lung weight (GMS)			Total lung capacity (CC)	
	Air[3]	0.75 ppm[3]	1.0 ppm[3]	Air[3]	0.75 ppm[3]	1.0 ppm[3]	Air[3]	0.75 ppm[3]
1	1.63 ± 0.29	1.61 ± 0.19	1.90 ± 0.62[1]	2.06 ± 0.48	1.79 ± 0.33	3.19[2] ± 0.84	14.28 ± 0.98	13.91 ± 0.72
3	1.47 ± 0.10	2.16 ± 0.42	2.00 ± 0.46	2.07 ± 0.16	2.52 ± 0.39	3.25[2] ± 0.73	14.32 ± 1.39	14.16 ± 0.88
7	1.65 ± 0.13	2.86[2] ± 0.54	3.60[2] ± 1.07	2.34 ± 0.45	2.40 ± 0.12	3.38[2] ± 0.46	14.13 ± 1.38	13.22 ± 0.99
14	1.61 ± 0.19	4.63[2] ± 0.97	4.06[2] ± 0.98	2.65 ± 0.51	2.29 ± 0.21	3.00 ± 0.54	12.67 ± 0.41	15.36[2] ± 1.98

[1] ± One standard deviation
[2] Significantly different from controls ($P < .05$)
[3] = 10 for all groups

ozone died between 7 and 14 days of exposure. The survivors th s represented the more resistant rats in the group.

The slope of the PV deflation curve was used as an index of the elastic properties of the lung. The intercept or lung volume at ambient pressure on the other hand bears a relationship to functional residual capacity. Significant changes in both of these parameters were detected after only one day exposure to 0.75 ppm ozone. Progressive changes, however, could not be detected with continued exposure. The PV curve after 14 days exposure appears to show a slight trend toward a return to control values. Thus, while alterations in the PV deflation curve were apparently more rapid than that of arterial blood gases or RV, they failed to provide a satisfactory index of progressive lung damage in the present study.

Pathological changes in the lungs of rats during short and intermediate term exposure to ozone have been described previously (Cavender *et al.*, 1977; Freeman *et al.*, 1974) and were evaluated primarily to confirm that expected changes had occurred. Decreases in PaO_2 generally corresponded to the severity of pulmonary pathology. In general, arterial blood gases were as sensitive as or more so than pulmonary function testing or examination of the lungs using light microscopy for the detection of lung damage by ozone.

The present findings are extremely pertinent to questions concerning the possible hazards of ozone exposure during high altitude flight. The concentrations selected for this study were somewhat greater than those occurring in areas with high concentrations of photochemical smog such as Los Angeles (U. S. Dept. Health Educ. and Welfare, 1970). Levels equal or even greater than those used here, however, may be reached or even exceeded for varying periods of time in cabins of high flying aircraft (Bennett, 1962). Moreover, intermittent exposure was reported to be almost as effective as continuous exposure in producing morphologic changes (Schwartz *et al.*, 1976).

The immediate safety of passengers and air crew members could thus be jeopardized if the concentration of ozone is sufficient to result in a lowering of PaO_2. Decreased blood oxygenation is a well known cause for impaired physical and mental performance. Furthermore, repeated exposure of air crew members to elevated ozone could result in chronic lung disease. Further studies are needed to delineate the effects of both continuous and intermittent exposure to ozone upon arterial blood gases and to relate these changes to physical and mental performance in both laboratory animals and humans.

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